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# Reduction in the population prevalence of hepatitis C virus viraemia among people who inject drugs associated with scale-up of direct-acting anti-viral therapy in community drug services: real-world data

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## ABSTRACT

**Background and aims** There has been little empirical evidence to show the ‘real-world’ impact of scaling-up direct-acting anti-viral (DAA) treatment among people who inject drugs (PWID) on hepatitis C virus (HCV) viraemia at a population level. We aimed to assess the population impact of rapid DAA scale-up to PWID delivered through community services—including drug treatment, pharmacies, needle exchanges and prisons—in the Tayside region of Scotland, compared with Greater Glasgow and Clyde (GGC) and the Rest of Scotland (RoS). **Design, setting and participants** Natural experiment, evaluated using data from national biennial surveys of PWID and national clinical data. Services providing injecting equipment (2010–18) and HCV treatment clinics (2017–18) across Scotland. A total of 12 492 PWID who completed a questionnaire and provided a blood spot (tested for HCV-antibodies and RNA); 4105 individuals who initiated HCV treatment. **Intervention and comparator, measurements** The intervention was rapid DAA scale-up among PWID, which occurred in Tayside. The comparator was GGC/RoS. Trends in HCV viraemia and uptake of HCV therapy over time; sustained viral response (SVR) rates to therapy by region and treatment setting. **Findings** Uptake of HCV therapy (last year) among PWID between 2013–14 and 2017–18 increased from 15 to 43% in Tayside, 6 to 16% in GGC and 11 to 23% in RoS. Between 2010 and 2017–18, the prevalence of HCV viraemia (among antibody-positives) declined from 73 to 44% in Tayside, 67 to 58% in GGC and 64 to 55% in RoS. The decline in viraemia was greater in Tayside [2017–18 adjusted odds ratio (aOR) = 0.47, 95% confidence interval (CI) = 0.30–0.75,  $P = 0.001$ ] than elsewhere in Scotland (2017–18 aOR = 0.89, 95% CI = 0.74–1.07,  $P = 0.220$ ) relative to the baseline of 2013–14 in RoS (including GGC). Per-protocol SVR rates among PWID treated in community sites did not differ from those treated in hospital sites in Tayside (97.4 versus 100.0%,  $P = 0.099$ ). **Conclusions** Scale-up of direct-acting anti-viral treatment among people who inject drugs can be achieved through hepatitis C virus (HCV) testing and treatment in community drug services while maintaining high sustained viral response rates and, in the Tayside region of Scotland, has led to a substantial reduction in chronic HCV in the population.

**Keywords** Hepatitis C, Chronic, direct-acting anti-virals, Viremia, sustained viral response, prevalence, Substance Abuse, Intravenous.

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## INTRODUCTION

In many countries, people who inject drugs (PWID) comprise the largest population of people infected with

hepatitis C virus (HCV), as well as the largest group at ongoing risk of infection [1]. In recognition of viral hepatitis as a global problem, the World Health Organization (WHO) has set targets to eliminate HCV, including an

80% reduction in HCV incidence by 2030 [2]. To achieve this target, countries will need to provide optimal coverage of harm reduction services (including needle and syringe programmes and opioid agonist therapy), but will also need to prioritize major scale-up (i.e. expansion) of HCV treatment for PWID [3–6]. Uptake of HCV therapy among PWID has been very limited until the recent introduction of direct-acting anti-viral therapies (DAAs)—highly effective, tolerable and simple-to-administer therapies for the treatment of HCV infection [7–9]. Further, there has been little empirical evidence to show the ‘real-world’ impact of scaling-up HCV DAA treatment among PWID on HCV viraemia at a population level [10–12].

In the Tayside region of Scotland an evaluation of the impact of major and rapid scale-up of DAAs among PWID is under way, involving the provision of HCV testing and treatment across the full range of community services engaged with this population, including drug treatment, pharmacies, needle exchanges and prisons [13]. The scale-up in Tayside, compared to other areas of Scotland, provides a unique opportunity to evaluate a natural experiment of the scale-up of DAAs on HCV viraemia prevalence in the PWID population.

Scotland is one of the few countries world-wide with comprehensive national surveillance systems, including large serial cross-sectional bio-behavioural surveys of PWID to monitor HCV infection and an HCV clinical database to monitor treatment outcomes [14,15]. Using these data, we assess the early impact of DAA scale-up in Tayside compared to other regions in Scotland. We aim to test the hypothesis that rapid scale-up of DAAs in community-based services translates into a decline in HCV viraemia among a population of PWID, and to test whether this rapid scale-up leads to any differences in sustained viral response (SVR) rates to therapy. Specifically, we examined: (i) the population-level prevalence of HCV therapy uptake, HCV viraemia and treatment-induced viral clearance among PWID over time and by region, (ii) the change in uptake of HCV therapy, HCV viraemia and treatment-induced viral clearance among PWID over time and by region and (iii) SVR rates by region, treatment setting and PWID status.

## METHODS

The current study forms one component of the ‘Evaluating the population impact of hepatitis C direct acting anti-viral treatment as prevention for people who inject drugs (EPIToPe)’ study, a mixed-methods evaluation of a natural experiment of HCV ‘Treatment as Prevention’ (TasP) among PWID [13]. The ‘intervention’ consists of the scale-up of DAAs and expansion of care pathways in National Health Service (NHS) Tayside (an administrative health region in Scotland), with other sites in Scotland

acting as the ‘controls’: NHS Greater Glasgow and Clyde (GGC) and the Rest of Scotland (RoS). NHS Tayside has an estimated 2700 PWID, which compares to 10 000 and 17 300 in GGC and RoS, respectively [13,16,17]. Prevalence of antibodies to HCV among PWID in Tayside in 2017–18 was 56% compared to 68% in GGC and 48% in RoS [14]. The scale-up in Tayside involves the treatment of at least 500 PWID over a 2–3-year period beginning in 2017; mathematical modelling has indicated that this has the potential to reduce the chronic HCV prevalence among PWID in Tayside from approximately 30 to 10% or less. In the rest of Scotland, financial considerations precluded rapid scale-up of treatment beyond those eligible via the fibrosis-based prioritization in place at the time.

The data analysed here relate to a time-point midway through scale-up, when approximately 200 PWID (i.e. 40% of the target) had been treated in community settings in Tayside. This study therefore evaluates the early impact of the DAA scale-up in Tayside. To address the aims described in the Introduction two sources of data were utilized, which are described further below and summarized in Box 1.

**Box 1. Summary of data sources.**

	<i>Data source</i>	
	<i>Needle Exchange Surveillance Initiative (NESI)</i>	<i>Hepatitis C clinical database</i>
Research aim addressed	(i) To determine the population-level prevalence of uptake of HCV therapy, HCV viraemia and treatment-induced clearance among PWID over time, comparing NHS Tayside with NHS GGC/RoS (ii) To examine the associations between region/year and uptake of HCV therapy, HCV viraemia and treatment-induced clearance among PWID	To determine SVR rates by region, treatment setting, and PWID status
Brief description	Serial cross-sectional bio-behavioural surveys of PWID recruited at sites that provide sterile injecting equipment across Scotland	National database holding information on patients attending 17 of the 18 HCV treatment clinics in Scotland (includes

(Continues)

Box 1. (Continued)

	<i>Data source</i>	
	<i>Needle Exchange Surveillance Initiative (NESI)</i>	<i>Hepatitis C clinical database</i>
Dates data collected	Survey sweeps undertaken in 2010, 2011–12, 2013–14, 2015–16, 2017–18	hospital, prison and community settings) January 2017–December 2018 (date of treatment commencement)
Measurements	HCV viraemia (HCV antibody-positive and HCV RNA-positive based on DBS results) HCV therapy (self-reported and only available for 2013–14 onwards) Treatment-induced viral clearance (combination of DBS result and self-reported HCV therapy, therefore only available for 2013–14 onwards)	ITT and per-protocol SVR
Comparators	Region: NHS Tayside versus NHS GGC versus RoS Time: survey year	PWID status Region: NHS Tayside versus NHS GGC versus RoS Treatment setting: hospital versus prison versus community
Analyses	(i) Proportions of respondents who reported ever/last year uptake of therapy, with HCV viraemia (imputed), and with treatment-induced viral clearance (imputed) by region and survey year (ii) Multi-level logistic regression to examine associations between region/survey year and uptake of therapy in the last year, HCV viraemia, and treatment-induced viral clearance	Proportions of respondents who achieved SVR by PWID status, region and treatment setting

HCV = hepatitis C virus; DBS = dried blood spot; GGC = Greater Glasgow & Clyde; HCV = hepatitis C virus; ITT = intention-to-treat; NHS = National Health Service; PWID = people who inject drugs; RNA = ribonucleic acid; RoS = Rest of Scotland; SVR = sustained viral response

## Data sources

### Needle exchange surveillance initiative (NESI)

NESI is a national bio-behavioural survey of PWID that has been undertaken approximately biennially since 2008–09 and covers an estimated 10–15% of the active PWID population in Scotland [14]. Recruitment takes place at sites that provide sterile injecting equipment across Scotland (some of which may also provide opioid agonist therapy); sites are chosen to be broadly geographically representative and approximately 100 sites are included per sweep, representing approximately 50% of all sites that provide injecting equipment in Scotland. Trained interviewers facilitate the completion of a questionnaire and take a blood spot sample from all consenting participants. Dried blood spots (DBS) are tested for antibodies to HCV and HCV RNA; methods have been described in detail previously [14,18]. Written informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval by the West of Scotland Research Ethics Committee (reference 08/S0709/46).

As part of EPIToPe, approximately 200 PWID had been treated in community settings in Tayside during 2017. As part of the NESI 2017–18 sweep, interviews in Tayside were carried out in early 2018. Thus, four sweeps of NESI (2010, 2011–12, 2013–14 and 2015–16) were undertaken prior to, and one (2017–18) following, the early scale-up of DAAs.

### Clinical database

The national Hepatitis C Clinical Database records clinical and epidemiological information on patients attending a specialist clinic for management of HCV infection and covers 17 of the 18 clinics in Scotland (consisting of clinics in hospitals, as well as nurse-led clinics in prisons and community settings) [15]. We extracted data (age, sex assigned at birth, injecting status, treatment dates, SVR achievement, treatment setting and clinic) regarding patients who commenced therapy between January 2017 and December 2018. Data were complete to 31 March 2019, so patients who commenced treatment at the end of December 2018 had sufficient time to complete treatment and have a follow-up SVR test.

## Measurements

### NESI

Based on the results of DBS testing, participants were categorized as HCV antibody-positive or -negative. Antibody positives were further classified as viraemic (HCV

antibody-positive and HCV RNA-positive) or cleared (HCV antibody-positive and HCV RNA-negative). In the latest three surveys (2013–14, 2015–16 and 2017–18), participants were asked if they had commenced drug therapy for their HCV infection ever or in the last year. Participants were further categorized into the groups indicated in Box 2 by combining their HCV infection status from their DBS test with their self-reported uptake of therapy. Those with cleared infection who reported receiving HCV therapy in the past (i.e. group A in Box 2) were defined as having ‘treatment-induced viral clearance’.

In order to generate appropriate denominators for HCV therapy uptake, we created definitions of individuals who were ‘eligible for therapy’. The denominator for those who had ever received therapy consisted of those with viraemia (i.e. groups B and D in Box 2) plus those who had cleared infection with evidence of therapy (i.e. group A). The denominator for therapy uptake in the last year consisted of those with viraemia (i.e. groups F and H in Box 2) plus those who had cleared infection with evidence of therapy in the last year (i.e. group E).

**Box 2. Classification of respondents into groups based on HCV antibody/RNA status combined with self-reported history of HCV therapy (ever and in the last year).**

	<i>HCV antibody-positive and HCV RNA-negative (cleared infection)</i>	<i>HCV antibody-positive and HCV RNA-positive (viraemic infection)</i>
Reported ever receiving therapy for HCV	Cleared infection through therapy (group A)	Viraemic (relating to either failed therapy or re-infection following therapy) (group B)
Did not report ever receiving therapy for HCV <sup>a</sup>	Cleared infection spontaneously (group C)	(group D)
Reported receiving therapy for HCV in the last year	Cleared infection through recent therapy (group E)	Viraemic (relating to either failed therapy or re-infection following recent therapy) (group F)
Did not report receiving therapy for HCV in the last year <sup>a</sup>	Cleared infection spontaneously or cleared through therapy more than one year ago (group G)	Viraemic (group H)

<sup>a</sup>Includes those who said they had not received treatment, as well as those who were unaware of their hepatitis C virus (HCV) infection.

### Clinical database

An SVR was defined as testing polymerase chain reaction (PCR)-negative for HCV RNA at either 24 weeks (pre-2014) or 12 weeks (2014 onwards) following completion of therapy, according to clinical guidelines [19]. The time-period is from the confirmed end of treatment (rather than the expected end of treatment) if a patient prematurely discontinues. Only patients who had a documented SVR at 24+ weeks (pre-2014) or 12+ weeks (2014 onwards) were considered to have a SVR. Intention-to-treat (ITT) SVR rates were calculated as the number of patients who achieved SVR as a proportion of the number of patients who commenced treatment. Per-protocol SVR rates were calculated as the number of patients achieving SVR as a proportion of the number of patients with an SVR outcome recorded (i.e. excluding unknown results).

### Statistical analysis

To describe the NESI participants, initial analyses looked at demographic and behavioural variables, by survey year and region: categorical variables were expressed as numbers and percentages, whereas continuous variables were presented as means or medians. To test for differences across surveys,  $\chi^2$  tests were performed for categorical variables and Wilk’s lambda was calculated for continuous variables.

The main statistical analyses undertaken are described below under headings that relate to the three aims described in the introduction.

### Population-level prevalence of uptake of HCV therapy, HCV viraemia and treatment-induced viral clearance (NESI data)

First, multiple imputation by chained equations (MICE) was applied to the NESI data to impute missing HCV antibody and HCV RNA results [20]. Missing data were assumed to be missing-at-random (MAR). This assumption, while not testable, was deemed plausible as there was no reason to believe that there was any systematic relationship between the absence of HCV antibody or HCV RNA measurement and the missing value. Survey year, region and time since onset of injecting were used as predictors in the imputation model and 20 imputed data sets were generated. Sensitivity analyses were performed by comparing the results from MICE to results generated from complete case analyses.

Where survey years were presented separately, NESI respondents who had participated more than once within a given survey year were identified (on the basis of initials, sex assigned at birth, date of birth and NHS Board of recruitment) and only their first interview/DBS was included in the analysis (when pooling data across the surveys,



participants who had participated multiple times across survey years were considered: see multi-level logistic regression).

The proportions of respondents in NESI who reported ever/last year uptake of therapy with viraemia and with treatment-induced clearance were compared across survey sweeps and NHS Board regions (Tayside/GGC/RoS). GGC was presented separately because it is the largest NHS board in Scotland (representing approximately 33% of individuals with problem drug use in Scotland and 40% of all NESI respondents in the included survey years) [17].

Additionally, the setting where HCV therapy was initiated among respondents in the 2017–18 survey was examined and a  $\chi^2$  test was performed to test for a difference in the proportion reporting community-initiated therapy by region.

#### *Associations of region and survey year with uptake of HCV therapy, HCV viraemia and treatment-induced viral clearance (NESI data)*

We used logistic regression to examine the association between the main predictors region and survey year and the outcomes uptake of therapy (in the last year), HCV viraemia (among antibody-positives) and treatment-induced viral clearance (among antibody-positives) in the NESI data collected from 2013–14 to 2017–18 (the models were restricted to these years because these were the only surveys in which the HCV treatment questions were asked). GGC was combined with RoS in these analyses to simplify the analysis of interactions between region and year. Univariable models were constructed for each predictor and outcome, followed by multivariable models also adjusted for sex (assigned at birth), age, time since onset of injecting, homelessness in the last 6 months (yes/no), receipt of methadone in the last 6 months (yes/no) and imprisonment in the last year (yes/no). Multivariable models were fitted with interactions between survey year and region and a likelihood ratio test (LRT) was conducted to test for evidence of the interaction. A multi-level regression modelling was used to take clustering and non-independence of observations among individuals into account, given that some individuals had participated more than once across the surveys (identified on the basis of initials, sex (assigned at birth), date of birth and NHS Board of recruitment).

#### *SVR rates by region, treatment setting and PWID status (clinical database)*

Where individuals had multiple courses of treatment, the SVR relating to the treatment episode with the most recent completion date was used in the analysis. ITT and

per-protocol SVR rates were calculated by PWID status, region (Tayside/GGC/RoS) and treatment setting (hospital/prison/community).

Analyses were undertaken in Stata version 13.1 [21]. Graphs were produced in Excel 2016 and R version 3.5.1 [22,23]. The analysis was not pre-registered on a publicly available platform, and therefore the results should be considered exploratory.

#### **Role of the funding source**

The funders had no role in the study design, data collection, data analysis, data interpretation, writing of the report or the decision to submit for publication.

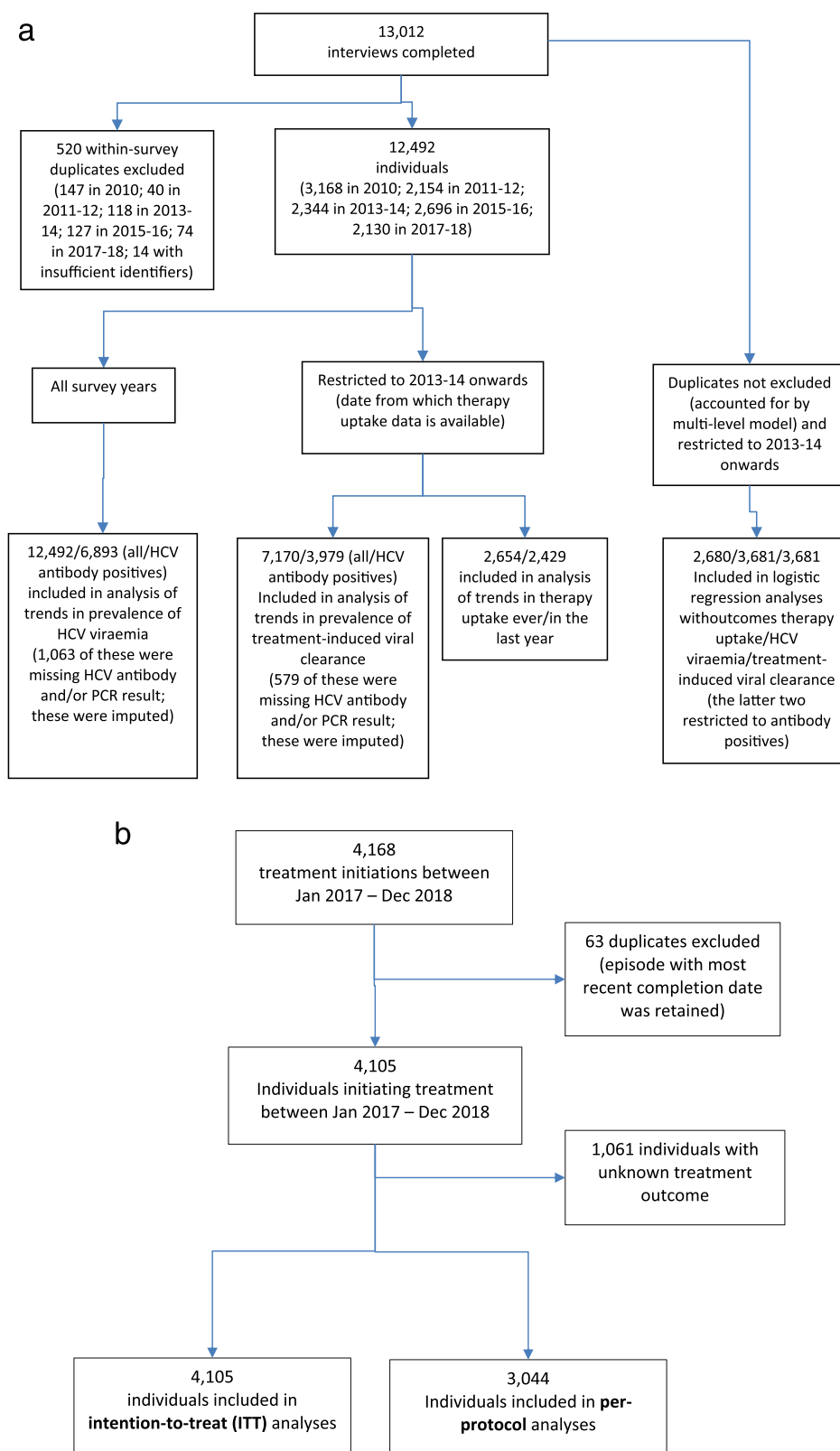
## **RESULTS**

A total of 12 492 PWID who participated in the NESI survey and 4105 individuals who initiated HCV treatment were included in this study. A further breakdown of the sample sizes that were included in the different analyses is given in Fig. 1a,b. An overview of the NESI samples recruited in Tayside, GGC and RoS are presented in the Supporting information, Tables S1–S3, respectively. The prevalence of HCV antibodies in Tayside ( $n = 818$ ), GGC ( $n = 5105$ ) and RoS ( $n = 6358$ ) ranged between 41–56, 63–69 and 44–52%, respectively, between 2010 and 2017–18. Approximately 70–80% of the sample were male, and this was consistent across the surveys and regions. Average age and time since onset of injecting increased across the surveys in all regions, suggestive of an ageing cohort effect. Excessive alcohol consumption was generally lower in Tayside compared with GGC and RoS (ranging from 10 to 19, 23 to 30 and 19 to 30%, respectively). Cocaine injection in the last 6 months was also generally lower in Tayside and showed evidence of an increase across the surveys in all regions (from 4 to 14% in Tayside, from 16 to 50% in GGC and from 7 to 19% in RoS).

#### *Population-level prevalence of uptake of HCV therapy, HCV viraemia and treatment-induced viral clearance (NESI data)*

In Scotland overall, the proportion of those who said they had ever received therapy or received therapy in the last year increased from 19% (167 of 863) and 9% (72 of 800) in 2013–14 to 38% (301 of 785) and 21% (144 of 680), respectively, in 2017–18 (Table 1). In Tayside, uptake of therapy in the last year increased from 15% (12 of 81) to 43% (26 of 61) between 2013–14 and 2017–18, compared with 6% (22 of 378) to 16% (50 of 322) in GGC and 11% (38 of 341) to 23% (68 of 297) in RoS.

Sensitivity analyses comparing the results from data imputation to results generated from complete case analyses are presented in the Supporting information, Table S4. Results were robust to these changes. Between



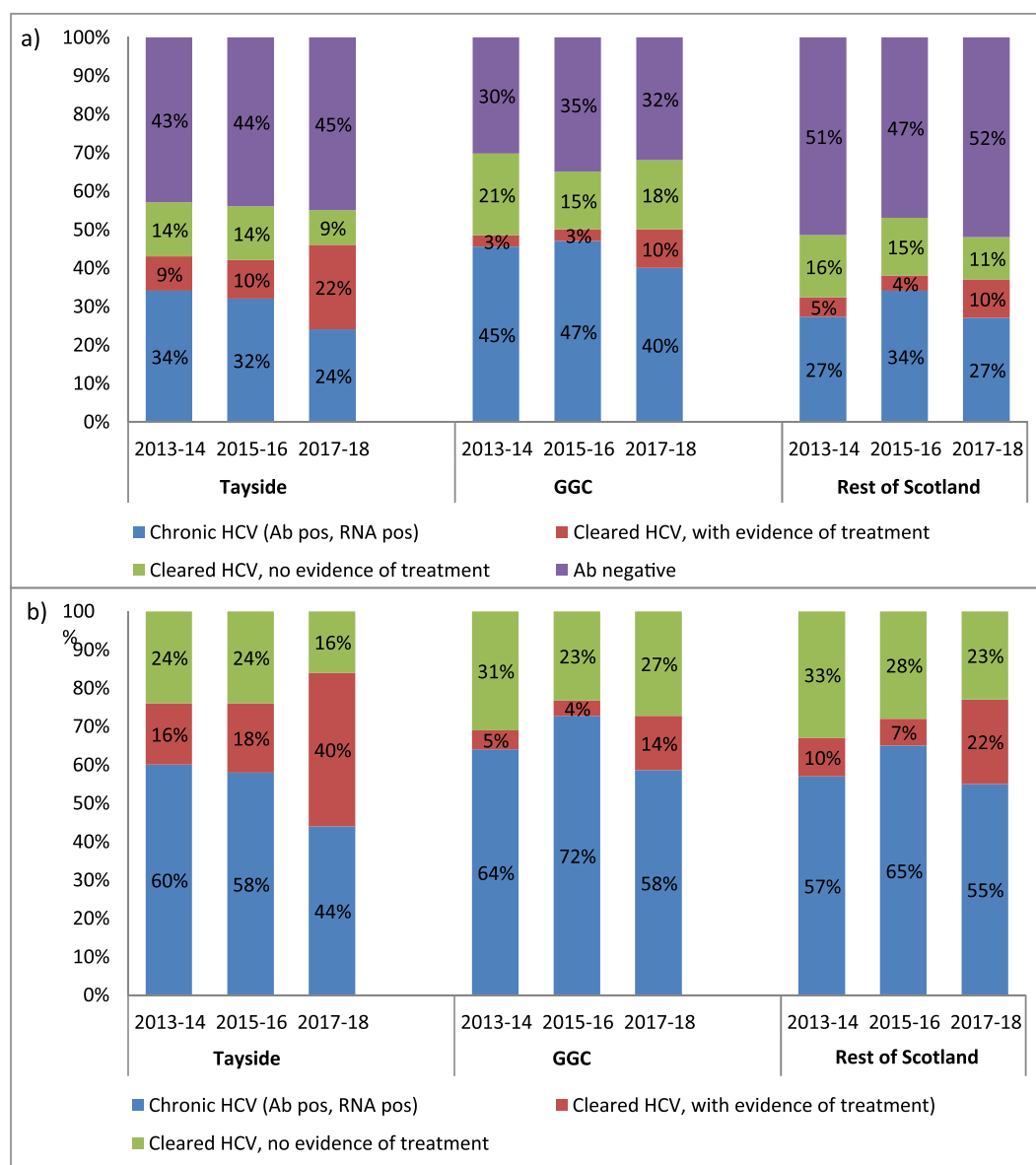
**Figure 1** (a) Number of participants included in the analysis of population-level prevalence of uptake of hepatitis C virus (HCV) therapy, HCV viraemia and treatment-induced viral clearance and the analysis of associations of region and survey year with uptake of HCV therapy, HCV viraemia and treatment-induced viral clearance (data from the Needle Exchange Surveillance Initiative/NESI). (b) Participants included in the analysis of sustained viral response (SVR) rates (data from the Scottish Hepatitis C Clinical Database)

**Table 1** Trends in uptake of HCV therapy and estimated prevalence of HCV viraemia and treatment-induced viral clearance among people who inject drugs attending injection equipment provision services across Scotland, 2010–18 (data from the Needle Exchange Surveillance Initiative/NESI).

		Survey sweep					
		Region	2010	2011–12	2013–14	2015–16	2017–18
Therapy uptake <sup>a</sup>	Ever	All Scotland	NA	NA	19% (167/863)	17% (171/1006)	38% (301/785)
		Tayside	NA	NA	31% (28/90)	35% (31/89)	65% (49/75)
		GGC	NA	NA	14% (54/399)	14% (57/422)	31% (111/360)
		Rest of Scotland	NA	NA	23% (83/374)	17% (83/495)	40% (141/350)
	Last year	All Scotland	NA	NA	9% (72/800)	7% (66/949)	21% (144/680)
		Tayside	NA	NA	15% (12/81)	23% (18/79)	43% (26/61)
		GGC	NA	NA	6% (22/378)	3% (13/406)	16% (50/322)
		Rest of Scotland	NA	NA	11% (38/341)	8% (35/464)	23% (68/297)
Prevalence of HCV viraemia <sup>b</sup>	All	All Scotland	37% (35–39%)	33% (31–35%)	35% (33–37%)	38% (36–40%)	32% (29–34%)
		Tayside	30% (24–36%)	24% (16–32%)	34% (27–40%)	32% (26–38%)	24% (18–30%)
		GGC	45% (42–47%)	39% (36–43%)	45% (41–48%)	47% (43–50%)	40% (36–43%)
		Rest of Scotland	31% (28–33%)	28% (25–31%)	27% (25–30%)	34% (31–36%)	27% (24–29%)
	HCV antibody-positives	All Scotland	66% (64–68%)	61% (58–64%)	60% (57–63%)	67% (64–69%)	55% (52–58%)
		Tayside	73% (64–82%)	59% (45–73%)	60% (51–69%)	58% (48–67%)	44% (34–55%)
		GGC	67% (64–70%)	62% (58–67%)	64% (60–68%)	72% (68–76%)	58% (54–63%)
		Rest of Scotland	64% (61–68%)	61% (56–65%)	57% (53–61%)	65% (61–68%)	55% (50–59%)
Prevalence of treatment-induced viral clearance <sup>b</sup>	All	All Scotland	NA	NA	5% (4–6%)	4% (3–5%)	11% (10–13%)
		Tayside	NA	NA	9% (5–13%)	10% (6–14%)	22% (16–27%)
		GGC	NA	NA	3% (2–4%)	3% (2–4%)	10% (8–12%)
		Rest of Scotland	NA	NA	5% (4–6%)	4% (3–5%)	10% (9–12%)
	HCV antibody-positives	All Scotland	NA	NA	8% (7–10%)	7% (6–8%)	20% (18–22%)
		Tayside	NA	NA	16% (9–23%)	18% (12–25%)	40% (30–49%)
		GGC	NA	NA	5% (3–6%)	4% (3–6%)	14% (11–17%)
		Rest of Scotland	NA	NA	10% (8–13%)	7% (5–9%)	22% (18–25%)

GGC = Greater Glasgow and Clyde; HCV = hepatitis C virus; NA = not applicable. <sup>a</sup>Among therapy-eligible respondents; see Methods for definitions. <sup>b</sup>Missing antibody and RNA data have been imputed; see Methods.





**Figure 2** Prevalence of viraemic and cleared HCV infection among people who inject drugs attending injection equipment provision services across Scotland, 2013 to 2018. Figures present (a) all respondents and (b) HCV antibody-positives only (data from the Needle Exchange Surveillance Initiative/NESI). Ab = antibody; GGC = Greater Glasgow and Clyde; HCV = hepatitis C virus; RNA = ribonucleic acid

2010 and 2017–18, the prevalence of HCV viraemia in Tayside decreased from 30% [95% confidence interval (CI) = 24–36%] in 2010 to 24% (95% CI = 18–30%) in 2017–18 among all respondents and from 73% (95% CI = 64–82%) to 44% (95% CI = 34–55%) among antibody-positives (Table 1 and Fig. 2). The latter compares to declines from 67% (95% CI = 64–70%) to 58% (95% CI = 54–63%) and 64% (95% CI = 61–68%) to 55% (95% CI = 50–59%) among antibody-positives in GGC and RoS, respectively.

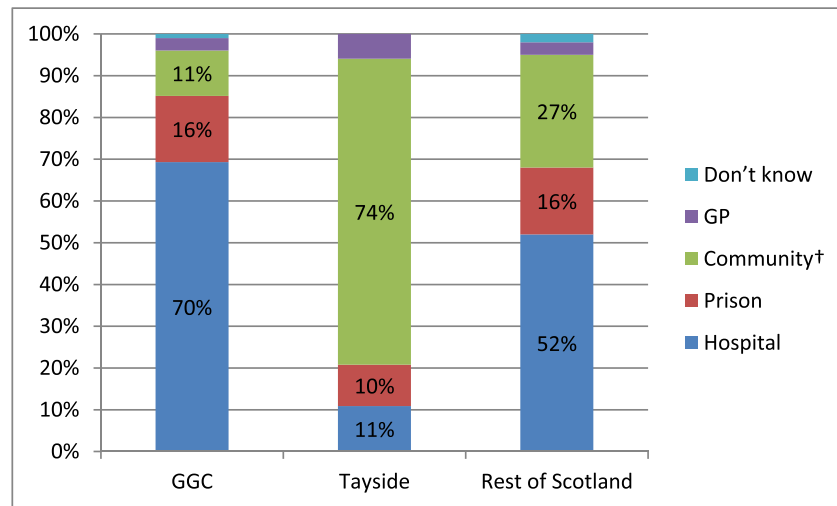
The prevalence of treatment-induced clearance (among antibody-positives) increased in Tayside from 16% (95% CI = 9–23%) to 40% (95% CI = 30–49%), in comparison to 5% (95% CI = 3–6%) to 14% (95%

CI = 11–17%) in GGC and 10% (95% CI = 8–13%) to 22% (95% CI = 18–25%) in RoS.

Figure 3 displays the setting where HCV therapy was initiated among respondents in the 2017–18 survey. A much larger proportion of respondents (74%, 62 of 84) in Tayside reported starting treatment in the community, compared with GGC (11%, 15 of 137) and RoS (27%, 52 of 190) ( $\chi^2 = 108.86$ ,  $P < 0.001$ ).

*Associations of region and survey year with uptake of HCV therapy, HCV viraemia and treatment-induced viral clearance (NESI data)*

PWID recruited in Tayside were more likely to have reported uptake of therapy, after adjustment for survey



**Figure 3** Site of initiation of most recent course of HCV therapy\* among people who inject drugs attending injection equipment provision services across Scotland, 2017–18 (data from the Needle Exchange Surveillance Initiative/NESI). GGC = Greater Glasgow and Clyde; GP = general practice; HCV = hepatitis C virus. \*Among those who had ever received HCV therapy; †includes needle exchanges, drug treatment sites, community health centres and at an individual's home

**Table 2** Logistic regression analyses of (a) uptake of therapy in the last year, (b) HCV viraemia (among HCV antibody-positives) and (c) treatment-induced viral clearance (among HCV antibody-positives), by region and survey year, among people who inject drugs attending injection equipment provision services across Scotland, 2013–2018<sup>a</sup> (data from the Needle Exchange Surveillance Initiative/NESI).

Outcome	Predictor	aORs <sup>a</sup>	
		aOR (95% CI)	P-value
Uptake of therapy (in last year) <sup>b</sup>	Rest of Scotland (including GGC)	(n = 2680)	
		2013–14	1
		2015–16	0.65 (0.44–0.97) 0.033
	Tayside	2017–18	2.35 (1.67–3.31) <0.001
		2013–14	2.12 (1.10–4.08) 0.025
		2015–16	2.87 (1.67–4.92) <0.001
HCV viraemia (among HCV antibody-positives)	Rest of Scotland (including GGC)	2017–18	5.19 (2.87–9.37) <0.001
		(n = 3681)	
		2013–14	1
	Tayside	2015–16	1.50 (1.27–1.77) <0.001
		2017–18	0.89 (0.74–1.07) 0.220
		2013–14	0.96 (0.64–1.44) 0.853
Treatment-induced viral clearance (among HCV antibody-positives)	Rest of Scotland (including GGC)	2015–16	0.57 (0.38–0.84) 0.005
		2017–18	0.47 (0.30–0.75) 0.001
		(n = 3681)	
	Tayside	2013–14	1
		2015–16	0.70 (0.51–0.96) 0.027
		2017–18	2.49 (1.88–3.30) <0.001
	Tayside	2013–14	2.46 (1.40–4.33) 0.002
		2015–16	4.37 (2.60–7.35) <0.001
		2017–18	4.12 (2.56–6.61) <0.001

aOR = adjusted odds ratio; CI = confidence interval; HCV = hepatitis C virus; GGC = Greater Glasgow and Clyde. <sup>a</sup>Adjusted odds ratios (aORs) derived from multivariable models with interaction effects (see supporting information, Table S5 for univariable and main effects models). Multivariable models are also adjusted for sex, age, time since onset of injecting, homelessness (last 6 months), receipt of methadone (last 6 months) and imprisonment (last year); <sup>b</sup>among therapy-eligible respondents; see Methods for definitions.

year and other variables [Supporting information, Table S5: adjusted odds ratio (aOR) = 3.13, 95% CI = 2.22–4.41]. While there was insufficient evidence for an interaction between year and region (likelihood ratio test/LRT,  $P = 0.112$ ), stratified analyses were suggestive of a larger increase in uptake of therapy in Tayside (aOR = 5.19, 95% CI = 2.87–9.37) compared with RoS (aOR = 2.35, 95% CI = 1.67–3.31), where the baseline for comparison was 2013–14 RoS (Table 2).

After adjustment, respondents in Tayside had lower odds of viraemia (aOR = 0.66, 95% CI = 0.52–0.84) compared with those in the rest of Scotland, with evidence of an interaction between region and year (LRT,  $P = 0.034$ ), indicating that there was a larger reduction in HCV viraemia in Tayside (aOR = 0.47, 95% CI = 0.30–0.75) compared with RoS (aOR = 0.89, 95% CI = 0.74–1.07), when compared to RoS 2013–14 (Table 2 and Supporting information, Table S5).

After adjustment, respondents in Tayside were more likely to have treatment-induced clearance (Supporting information, Table S5: aOR = 3.57, 95% CI = 2.65–4.81) compared with those in the rest of Scotland. There was insufficient evidence of an interaction between region and year (LRT,  $P = 0.254$ ), but some evidence of a larger increase in treatment-induced clearance in Tayside (aOR = 4.12, 95% CI = 2.56–6.61) compared with RoS (aOR = 2.49, 95% CI = 1.88–3.30) (Table 2).

#### *SVR rates by region, treatment setting and PWID status (clinical database)*

There was a difference of approximately 6–8 percentage points in ITT rates between PWID and non-PWID in GGC (74 versus 81%,  $P = 0.007$ ), RoS (66 versus 72%,  $P = 0.008$ ) and Tayside (78 versus 86%,  $P = 0.119$ ) (Table 3, Fig. 4, Supporting information, Fig. S1). In all Scottish regions, per-protocol SVR rates did not differ significantly between PWID and non-PWID. There was evidence that ITT SVR rates were lower in community settings compared with hospital settings in GGC (70 versus 80%,  $P < 0.001$ ), RoS (65 versus 72%,  $P = 0.01$ ) and Tayside (78 versus 85%,  $P = 0.121$ ). Per-protocol SVR rates did not differ significantly across treatment settings in any Scottish regions.

## DISCUSSION

In this study, we found that rapid scale-up of DAAs among PWID in community settings in Tayside led to a greater decline in the prevalence of viraemic infection among PWID than elsewhere in Scotland. There was also evidence that HCV viraemia declined, to a lesser extent, in other sites in Scotland correlated with increases in HCV treatment. Further, we found that the

increase in community treatment in Tayside was not associated with any reduction in SVR rates in per-protocol analyses.

While numerous mathematical modelling studies have examined the hypothetical impact of scaling-up HCV therapy on chronic HCV prevalence, there has been little empirical evidence to corroborate these models [11–13]. One study has examined the impact of DAAs on chronic HCV prevalence at a subnational level (in prisons) [24]. Other 'real-world' evidence published focuses upon scaling-up treatment and SVR, rather than impact at a population level [25–27]. To our knowledge, only one other study to date has used national data to examine the impact of treatment scale-up among PWID on viraemic prevalence at a population level. They found that treatment uptake (ever) among Australian PWID increased from 10 to 41%, and that viraemic prevalence decreased from 43 to 25% overall, between 2015 and 2017 [10]. However, direct comparisons with Australia cannot be drawn, given the different interventions: they evaluated the impact (pre versus post) of the introduction of completely unrestricted access to DAAs across the country, whereas we evaluated an intervention (that had been demonstrated in mathematical models to deliver population-level change in HCV viraemia) involving scale-up of DAAs in a specific PWID population, compared with a natural control group, through delivery of therapy across multiple community-based settings. Further, a limitation recognized in the Australian study was the amount of missing RNA results from DBS testing (44–60% of antibody-positive samples across the 3 years of data), which may have led to bias within their analysis, compared in our study to 4–11% missing RNA results.

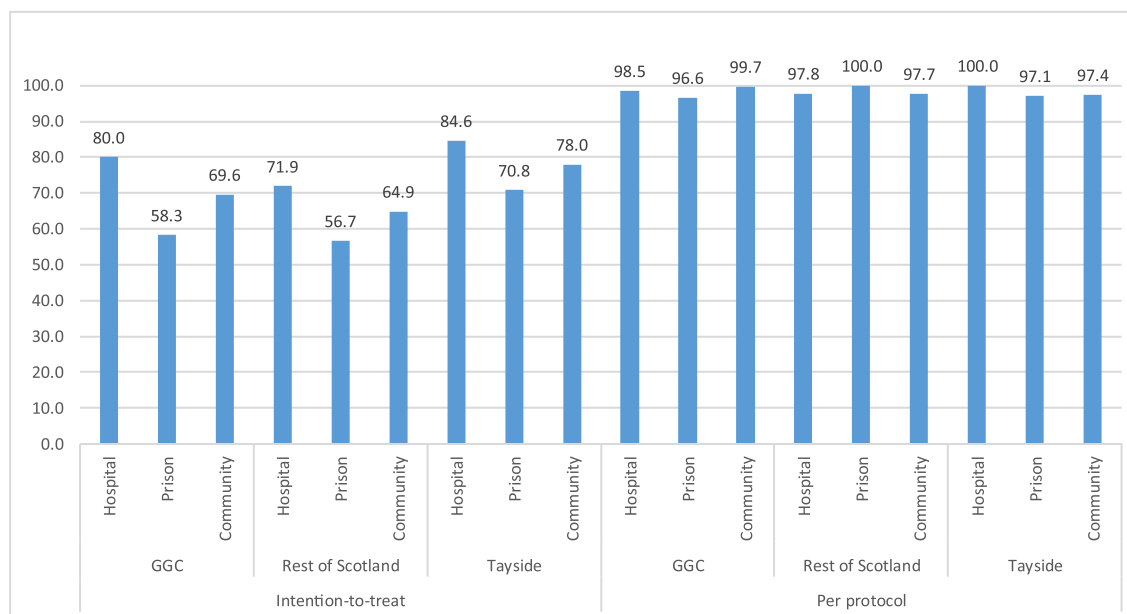
It is notable that treatment interventions had been occurring in Tayside prior to EPIToPe, albeit to a much lesser extent, with approximately 100 PWID treated with interferon-based therapies during 2012–16 [28]. These treatment interventions may account for the higher uptake of therapy at 'baseline' (i.e. pre-EPIToPe scale-up) in Tayside compared with other regions. However, while these early interventions did not constitute 'rapid' scale-up, they can nevertheless be considered as part of the package of treatment interventions delivered to PWID in Tayside and their impact can be seen pre-2017–18. We have demonstrated the impact of partial scale-up; future sweeps of NESI will allow us to measure further progress towards reducing viraemia to 10% or lower.

DAA scale-up is one of the key tools for countries to achieve HCV elimination. In their strategy for elimination of viral hepatitis, the WHO have set targets relating to incidence of HCV infection, but not for prevalence viraemia/chronic infection [2]. We believe that monitoring impact on prevalence of viraemia is a necessity to evaluate the direct, short-term impact of DAA scale-up, as any

**Table 3** Intention-to-treat/per-protocol SVR rates by region, PWID status and treatment setting among patients initiated on HCV therapy in Scotland during 2017–18 (data from the Hepatitis C clinical database).

	Region	PWID <sup>d</sup>		Non-PWID <sup>d</sup>		$\chi^2$ , P-value		
		n/N	% (95% CI)	n/N	% (95% CI)			
Intention-to-treat	All Scotland	2227/3111	71.6% (70.0–73.2%)	765/994	77.0% (74.2–79.5%)	11.021, P = 0.001		
	Tayside	343/441	77.8% (73.6–81.6%)	61/71	85.9% (75.6–93.0%)	2.433, P = 0.119		
	GGC	1099/1477	74.4% (72.1–76.6%)	345/427	80.8% (76.7–84.4%)	7.379, P = 0.007		
	Rest of Scotland	785/1193	65.8% (63.0–68.5%)	359/496	72.4% (68.2–76.3%)	6.937, P = 0.008		
Per-protocol	All Scotland	2227/2267	98.2% (97.6–98.7%)	765/777	98.5% (97.3–99.2%)	0.167, P = 0.683		
	Tayside	343/351	97.7% (95.6–99.0%)	61/61	100% (94.1–100%)	1.418, P = 0.234		
	GGC	1099/1112	98.8% (98.0–99.4%)	345/352	98.0% (96.0–99.20%)	1.333, P = 0.248		
	Rest of Scotland	785/804	97.6% (96.3–98.6%)	359/364	98.6% (96.8–99.6%)	1.219, P = 0.270		
	Region	Hospital		Prison		Community <sup>b</sup>		$\chi^2$ , P-value (comparing community versus hospital)
		n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	
Intention-to-treat	All Scotland	1923/2507	76.7% (75.0–78.3%)	207/349	59.3% (54.0–64.5%)	841/1194	70.4% (67.8–73.0%)	16.815, P < 0.001
	Tayside	104/123	84.6% (76.9–90.4%)	34/38	70.8% (55.9–83.1%)	266/341	78.0% (73.2–82.3%)	2.398, P = 0.121
	GGC	1038/1297	80.0% (77.8–82.2%)	84/144	58.3% (49.8–66.5%)	322/463	69.6% (65.1–73.7%)	21.356, P < 0.001
	Rest of Scotland	781/1087	71.9% (69.1–74.5%)	89/157	56.7% (58.6–64.6%)	253/390	64.9% (59.9–69.6%)	6.655, P = 0.010
Per-protocol	All Scotland	1923/1957	98.3% (97.6%–98.8%)	207/211	98.1% (95.2–99.5%)	841/855	98.4% (97.3–99.1%)	0.035, P = 0.851
	Tayside	104/104	100.0% (96.5–100.0%)	34/35	97.1% (85.1–99.9%)	266/273	97.4% (94.8–99.0%)	2.717, P = 0.099
	GGC	1038/1054	98.5% (97.6–99.1%)	84/87	96.6% (90.3–99.3%)	322/323	99.7% (98.3–100.0%)	2.961, P = 0.085
	Rest of Scotland	781/799	97.8% (96.5–98.7%)	89/89	100.0% (95.9–100.0%)	253/259	97.7% (95.0–99.2%)	0.004, P = 0.952

CI = confidence interval; GGC = Greater Glasgow and Clyde; HCV = hepatitis C virus; PWID = people who inject drugs; SVR = sustained viral response. <sup>a</sup>Patient had indicated ever injecting drugs. <sup>b</sup>Community sites include needle exchanges, pharmacies, drug treatment centres and other outreach clinics.



**Figure 4** Intention-to-treat/per-protocol SVR rates by region and treatment setting among patients attending specialist liver clinics in Scotland, 2017–18 (data from the Hepatitis C clinical database). GGC = Greater Glasgow and Clyde; SVR = sustained viral response

increase in recent therapy uptake would be directly observable in viraemic prevalence. We acknowledge that is nevertheless important, in the longer term, to monitor incidence, as this can also impact upon viraemic prevalence. In particular, incidence of HCV re-infection is a key consideration with regard to HCV elimination among PWID: if population-level viremia is not rapidly reduced to sufficiently low levels, then re-infections will cause a rise in the HCV viraemic prevalence [29]. Future analyses examining the impact of full scale-up in Tayside will consider both primary incident infections and re-infections.

We have also provided evidence that rapidly scaling-up treatment to people through community drug services (and who are therefore probably continuing to inject either during and/or after therapy) does not compromise SVR rates. Although the intention-to-treat SVR rates were lower in community sites (compared with hospital) and among PWID, this is probably a result of PWID not attending their appointment for confirmation of SVR and is therefore a reflection of lack of follow-up rather than lack of SVR attainment [30]. The latter is corroborated by NESI data from Tayside in 2017–18 which show that, of those who said that they had been initiated on treatment in the last year (who we can assume are a mixture of individuals who did/did not return for a confirmatory SVR test), 96% were PCR-negative (95% CI = 81–99%). Non-compliance is nevertheless a concern, as there is evidence to suggest poor health outcomes among non-compliant individuals; however, they represent a small minority of the patients who commence therapy [31]. Although the DAAs are highly tolerable, easy to take/administer and involve a much shorter course of treatment than the

interferon-based therapies, compliance can nevertheless be challenging for individuals with complex personal and social circumstances [30].

A major strength of our analysis is the ‘natural experiment’ design, whereby Tayside represents the ‘intervention’ group and GGC/RoS are the ‘control’ group. A further strength of our study is the data sources, which are comprehensive and national: few countries are in a position to be able to measure population-level changes in HCV viraemia among PWID, NESI being one of only four serial bio-behavioural studies of its kind internationally [10,32,33]. However, we acknowledge several limitations. First, we relied upon self-report for uptake of HCV therapy, which may be subject to recall and social desirability biases. Secondly, there is sampling variation between the serial surveys and could be a potential reason for differences between the survey sweeps. However, most sample characteristics were relatively stable across the period examined or followed expected trends—such as the increase in cocaine injecting [34]. Thirdly, there were variations in prevalence of HCV antibody in Tayside, which was 41–42% in 2010–12 and increased to 56% in 2013–14. These changes may result from selection bias because, as part of the intervention, treatment became available at some of the needle exchange and drug treatment settings where NESI recruitment takes place, potentially attracting more hepatitis C-infected clientele, thereby artificially increasing the prevalence [28,35]. To account for this issue, we analysed and presented the viraemia data among HCV antibody-positives, which removed any variation in overall antibody prevalence (we have also presented the prevalence of viraemia among all respondents for comparison



purposes). We acknowledge that this selection bias could also have affected the rates of treatment uptake and viraemia itself for the same reasons. However, if we examine the distribution of settings where individuals initiated treatment from the clinical database (which captures a comprehensive picture of all those receiving treatment), 24, 9 and 67% of treatment initiations in Tayside in 2017–18 occurred in hospitals, prisons and community settings, respectively. Comparing that to the distribution obtained from NESI respondents recruited in Tayside shows that the oversampling from community settings, while not insignificant, is not vast (with 11, 10 and 79% of treatment initiations in 2017–18 in hospitals, prisons and community settings, respectively). A fourth limitation of the study relates to the assays used to detect HCV antibody and RNA on DBS. The sensitivity and specificity of the antibody test are 99 and 100%, respectively; the corresponding values for the PCR test are 100 and 96% [36,37]. There is therefore a very small chance of false negatives or false positives on both tests. We may have missed individuals who had very recently been infected, given that antibody and RNA levels may fall below the lower limits of detection during this time [38]. However, these are likely to be very small numbers and should therefore not affect our viraemic prevalence estimates [18]. Finally, the incomplete treatment data was a limitation and is reflected in the ITT SVR rates as they include missing confirmatory tests.

In conclusion, we have demonstrated the feasibility and effectiveness of an approach that involves HCV testing and treatment in a range of community services engaged with PWID in increasing HCV treatment uptake and thereby reducing the prevalence of HCV viraemia. Our findings provide compelling evidence for other countries to plan their HCV elimination strategies.

#### Declaration of interests

S.J.H. has received honoraria from Gilead, outside the submitted work. J.E.D. declares research grants, in part supporting the scale-up of HCV treatment in Tayside, from AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharpe and Dohme and Roche and other research grants and honoraria for lectures from AbbVie, Abbott, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharpe and Dohme and Roche, outside the submitted work. P.H. has spoken or been on advisory boards for AbbVie, BMS, Eisai Ltd, Falk, Ferring, Gilead, Gore, Janssen, Lundbeck, MSD, Norgine, Novartis, ONO Pharmaceuticals, Pfizer and Roche. All other authors declare no competing interests.

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#### Author contributions

**Andrew McAuley:** Investigation; methodology; project administration. **John Dillon:** Conceptualization; data curation; funding acquisition. **Scott McDonald:** Formal analysis; methodology. **Alan Yeung:** Data curation; formal analysis. **Shanley Smith:** Data curation; resources. **Stephen Barclay:** Data curation; investigation. **Peter Hayes:** Data curation; investigation. **Samantha Shepherd:** Data curation; validation. **Rory Gunson:** Data curation; validation. **David Goldberg:** Conceptualization; data curation; funding acquisition; investigation. **Matthew Hickman:** Conceptualization; funding acquisition; investigation; methodology. **Sharon Hutchinson:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology.

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### Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Sample demographics, behaviours and serological results among people who inject drugs attending injection equipment provision services 2010–2018, **Tayside NHS Board** (data from the Needle Exchange Surveillance Initiative/NESI).

**Table S2.** Sample demographics, behaviours and serological results among people who inject drugs attending injection equipment provision services, 2010–2018, **Greater Glasgow & Clyde NHS Board** (data from the Needle Exchange Surveillance Initiative/NESI).

**Table S3.** Sample demographics, behaviours and serological results among people who inject drugs attending injection equipment provision services 2010–2018, **rest of Scotland** (data from the Needle Exchange Surveillance Initiative/NESI).

**Table S4.** Sensitivity analyses comparing multiply imputed data versus complete case analysis: prevalence of viraemic HCV infection.

**Table S5.** Logistic regression analyses of associations of region and survey year with a) uptake of therapy in the last year, b) HCV viraemia (among HCV antibody positives) and c) treatment-induced viral clearance (among HCV antibody positives), among people who inject drugs attending injection equipment provision services across Scotland, 2013–2018.\*

**Figure S1.** Intention-to-treat/per-protocol SVR rates by PWID status among patients attending specialist liver clinics in Scotland, 2017–2018.